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Gómez–López–Hernández syndrome: reappraisal of the diagnostic criteria

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Abstract Gómez–López–Hernández syndrome (GLHS) is a rare and possibly underdiagnosed condition. So far, 21 patients have been reported and all of them were sporadic observations. We report six additional patients. The hallmark triad of GLHS, also named cerebellotrigeminal dermal dysplasia, consists of rhombencephalosynapsis, trigeminal anesthesia (often giving rise to corneal opacities), and bilateral parietal or parieto-occipital alopecia. Our patients had rhombencephalosynapsis and alopecia, but none had trigeminal dysfunction. In this respect, the term cerebellotrigeminal dermal dysplasia is potentially misleading. In conclusion, only rhombencephalosynapsis and alopecia are consistently present in GLHS and are required diagnostic criteria, while trigeminal anesthesia, dysmorphic features, and ataxia are inconsistent findings. A high index of suspicion is required to diagnose GLHS, particularly as alopecia tends to be hidden by surrounding scalp hair.

Keywords Gómez–López–Hernández syndrome · Alopecia · Ataxia · Trigeminal anesthesia · Rhombencephalosynapsis

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Introduction

Gómez–López–Hernández syndrome (GLHS; MIM 601853), also called cerebellotrigeminal dermal dysplasia, is a rare syndrome characterized by the triad of rhombencephalosynapsis, trigeminal anesthesia, and bilateral parietal or parieto-occipital alopecia [4, 15]. Rhombencephalosynapsis is defined by absence of the cerebellar vermis, fusion of the cerebellar hemispheres across the midsagittal plane (best seen as abnormal horizontal orientation of the cerebellar folia on posterior coronal images), dentate nuclei appearing as an almost single structure consisting of contributions by left and right hemispheres, and fusion of the superior cerebellar peduncles. Inconsistent additional features of GLHS include craniofacial dysmorphic signs (such as a brachy-turriccephaly (without craniosynostosis), midface hypoplasia because of underdeveloped malar and maxillar bones (giving rise to downward slanted palpebral fissures and relative prognathism), hypertelorism, low-set, posteriorly rotated ears, ptosis, broad nasal tip, thin upper vermillion, and downturned corners of the mouth), strabismus, short stature, and corneal opacities secondary to trigeminal anesthesia. Cognitive functions are usually impaired, but four patients without cognitive impairment have been described [11, 15, 17, 23].

Recently, we reported four patients calling attention to the observation that the diagnosis is easily missed [15]. Currently, we are aware of 21 published patients [2–6, 10, 11, 15, 17, 18, 20, 23, 25]. The aim of this study is (1) to describe six additional patients, four were diagnosed in Armenia following a teaching course on cerebellar malformations, and (2) to reappraise the value of the traditional (diagnostic) triad.

Table 1 Clinical and neuroimaging findings in six patients with Gómez-López-Hernández syndrome

Patients	1	2	3	4	5	6
Sex	Male	Male	Male	Male	Male	male
Nationality	Armenian	Armenian	Armenian	Armenian	Swiss	Swiss-Polish
Age at first signs and symptoms	Neonate	Infant	Infant	Infant	Neonate	Infant
First signs and symptoms	Feeding problems	Global dev. delay	Floppy child	Ventriculomegaly	Hydrocephalus	Motor dev. delay
Age at study (years)	12	7	2	20	1.5	12
Brain MRI						
	Rhombencephalosynapsis					
	Other abnormalities	+	+	+	+	+
Central nervous system	Truncal ataxia	–	–	Mild <i>vm</i> , cleft ^b	Hydrocephalus	–
	Dysmetria	–	n.a.	–	n.a.	–
	Muscular hypotonia	+	n.a.	–	n.a.	–
	Head nodding	+	+	–	+	–
	Trigeminal anesthesia	+	+	+	–	+
	Corneal opacities	–	–	–	–	–
Craniofacial	Cognitive functions	–	–	–	–	–
	Perf. IQ=59	Perf. IQ=78	Normal development	Full-scale IQ=90	EQ 90	Full-scale IQ=114
	Temporal ^a	Parietal right, temporal left	Parietal	Temporal	Temporal	Temporal
	Alopecia	–	+	+	+	–
	Brachycephaly	–	–	+	+	–
	Midface hypoplasia	+	–	+	+	–
	Hypertelorism	–	–	–	+	–
	Low-set, posteriorly rotated ears	+	+	–	+	–
Growth	Short stature ($P<3$)	+	–	–	–	–
Additional signs	Nasal voice, mild ptosis, strabismus, cryptorchidism, relative prognathism	Strabismus, epileptic seizures, agenesis of the right kidney	Strabismus	Mild ptosis	–	Nasal Voice

Dev. developmental, EQ developmental age, IQ intelligence quotient, *vm* ventriculomegaly^a Additional small areas of alopecia in the vertex area^b Cleft in the left brainstem–cerebellar junction

Patients and methods

Patients

Between April and November 2009, we diagnosed GLHS in six new patients. In four of them (patients 1–4), the diagnosis was made after a teaching course in Armenia. Patients 5 and 6 are of Swiss and Swiss-Polish origin, respectively. All patients in this series are males. There was no parental consanguinity. Two patients presented neonatally with feeding problems and hydrocephalus. In the other four children, the first symptoms appeared in infancy as global or motor developmental delay, marked muscular hypotonia, and ventriculomegaly. At the time of this study, the median age was 9.5 years (range 1.5 to 20 years).

Methods

Cognitive impairment was defined as an IQ of <70. Cognitive functions were tested in four patients according to age with the non-verbal part of the Kaufman Assessment Battery for Children-II ($n=2$); currently, there is no validated Armenian verbal part of this test [9], Hamburg-Wechsler-Intelligenztest für Kinder III ($n=1$) [21], and Wechsler Intelligenztest für Erwachsene III ($n=1$) [24]. In one infant (patient 5), the developmental age was tested using the third edition of the Griffith mental developmental scales. Patient 3 was not formally tested: Information about his development has been obtained from history and clinical observations.

Results

The relevant clinical and neuroimaging data are summarized in Table 1.

Typical signs of *rhombencephalosynapsis* were present in all patients. Additionally, the MRI of patient 4 showed a cleft at the left brainstem–cerebellar junction (Fig. 1). Other neuroimaging abnormalities included ventriculomegaly and hydrocephalus due to stenosis of the Sylvian aqueduct in one patient.

Ataxia (truncal and limb) was found only in one patient, while muscular hypotonia and horizontal side-to-side head nodding were present in four patients.

Cognitive functions could be assessed in four patients. In two patients, full-scale IQ was measurable and was normal in both cases (90 and 114, respectively). In patient 6, verbal IQ was 106 and performance IQ 120. In patients 1 and 2, only performance IQ could be assessed (59 and 78, respectively). Due to his young age, in one patient, only developmental age, not IQ, could be assessed and this was normal (EQ 90). Cognitive development of patient 3 could not be formally tested, but information obtained from history and clinical observations showed normal development at the age of 2 years.

Bilateral alopecia was present from birth in all patients. It was bitemporal in four cases (Figs. 2b, 3b, and 4a, b), temporal on one side and parietal on the other in one, and biparietal in one boy. Patient 1 had additional small areas of alopecia frontally and in the region of the vertex (Fig. 2a). In three patients, the alopecia could be perfectly hidden by the surrounding hairs, and in three cases, it was asymmetric. Interestingly, patient 4 had an assisted birth with forceps, and bilateral alopecia has been interpreted as residual after forceps delivery.

Trigeminal sensation was normal in all patients, corneal reflexes could be elicited in all cases, and corneal opacities were not detectable in any patient.

Craniofacial dysmorphic signs were present in five of six patients: midface hypoplasia (Figs. 2b and 3b) and low-set, posteriorly rotated ears (Fig. 2b) in four, brachycephaly

Fig. 1 Brain MRI of patient 4 at the age of 20 years. **a** Axial T2-weighted MRI showing fusion of the cerebellar hemispheres with no intervening vermis and a cleft in the left brainstem–cerebellar junction (white arrows). **b** Posterior coronal T1-weighted MRI demonstrating fused cerebellar hemispheres, abnormal horizontal orientation of cerebellar folia, and ventriculomegaly

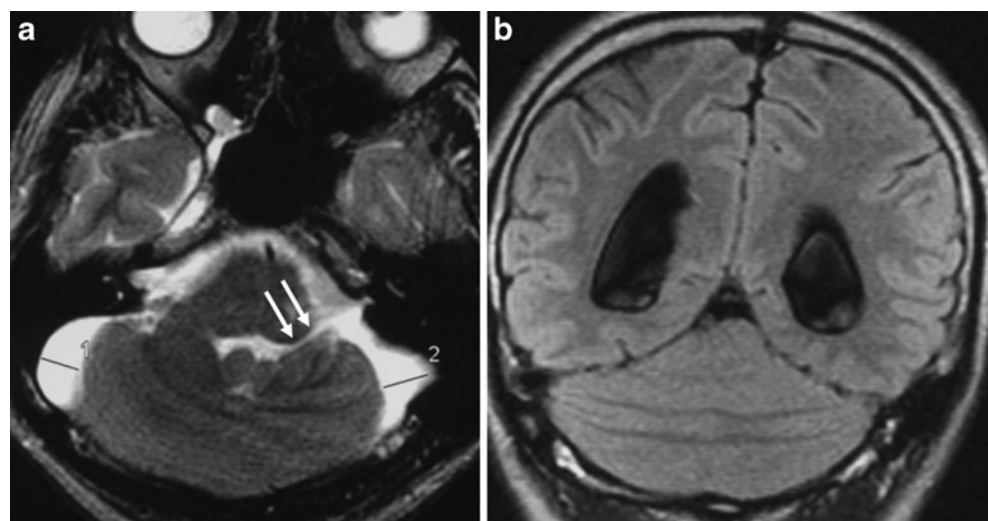
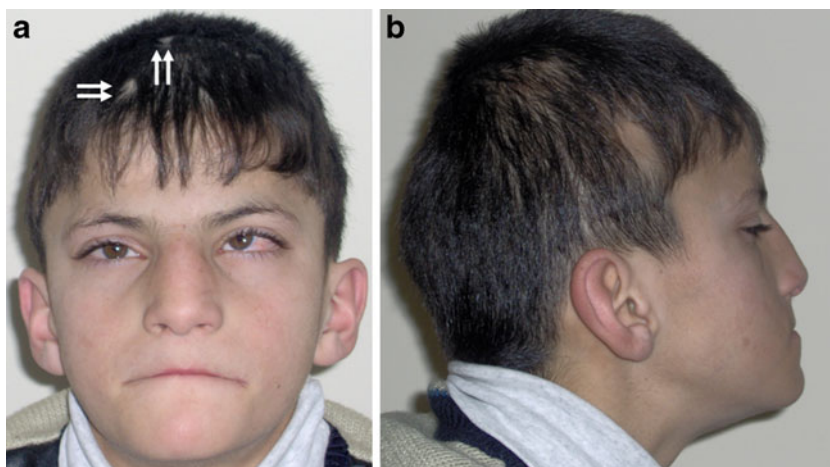


Fig. 2 Patient 1 at the age of 12 years. **a** Front view showing broad forehead, mild bilateral ptosis, strabismus, prominent nose, and small areas of alopecia frontally and in the vertex area (white arrows). **b** Right side view revealing low-set, posteriorly rotated ears, relative prognathism, midface hypoplasia, and temporal alopecia



(Fig. 3b) and strabismus in three, bilateral mild ptosis in two (Figs. 2a and 3a), and hypertelorism and relative prognathism (Fig. 2b) in one.

Discussion

Gómez-López-Hernández syndrome is a rare, sporadic syndrome and is likely to be underdiagnosed. Parental consanguinity was reported only in one of 27 patients [6]. Males are markedly more likely to be affected than females (19 males, eight females), but in terms of disease severity, we did not find a gender-related difference. So far, genetic analyses (karyotype, CGH arrays) have not yielded abnormal results for GLHS, or for isolated rhombencephalosynapsis either. All patients (GLHS and rhombencephalosynapsis) are sporadic observations. Therefore, either spontaneous dominant mutations or de novo chromosomal rearrangements are possible explanations [15]. From this point of view, GLHS is

an excellent candidate to be used in a total exome sequencing project. It is not certain whether GLHS and (isolated) rhombencephalosynapsis are different entities, or whether they represent a disease spectrum. Therefore, at this point, both rhombencephalosynapsis and GLHS need to be further defined by neuroimaging and other clinical features, respectively.

According to MIM catalogue and literature reports, GLHS is characterized by a triad including rhombencephalosynapsis, bilateral parietal or parieto-occipital alopecia, and trigeminal anesthesia. Typical additional findings include several craniofacial dysmorphic signs (brachy-turriccephaly, midface hypoplasia, hypertelorism, and low-set, posteriorly rotated ears) and neurological findings (ataxia, muscular hypotonia, cognitive impairment, and strabismus).

Rhombencephalosynapsis constitutes a consistent key feature of GLHS and was reported in all but one case (not reported in the first description by Gómez because neuro-

Fig. 3 Patient 4 at the age of 20 years. **a** Front view showing broad, high forehead, mild bilateral ptosis, and slight synophris. **b** Left side view demonstrating brachy-turriccephaly, midface hypoplasia, and temporal alopecia

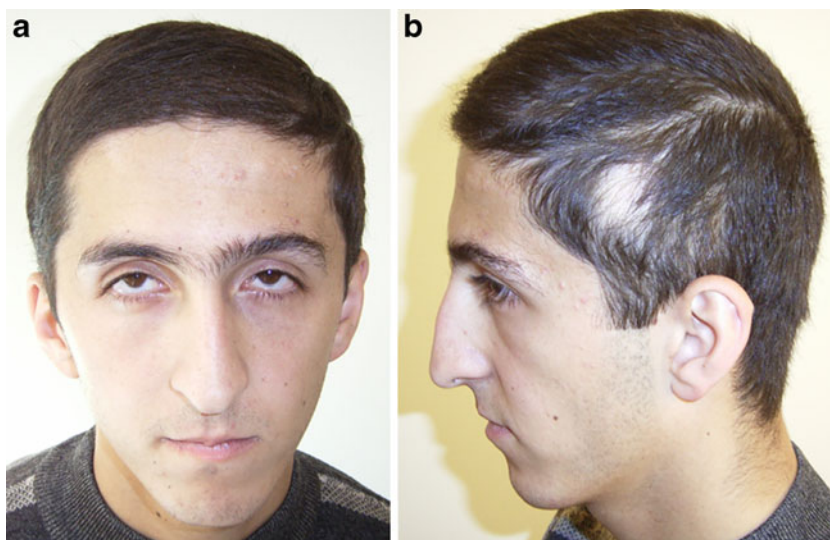


Fig. 4 Patient 6 at the age of 12 years. **a** Right side view showing temporal alopecia. **b** Left side view revealing less pronounced temporal alopecia. Ears and midface were normal



imaging studies had not been performed). Rhombencephalosynapsis mostly occurs in isolation but may be associated with other brain anomalies such as hydrocephalus, aplasia of the septum pellucidum, hypoplasia of the corpus callosum, hippocampal abnormalities, and fusion of the fornices [14, 22]. In this series, we found a cleft at the left brainstem–cerebellar junction in one patient. There are no previous reports of a similar neuroimaging finding in rhombencephalosynapsis, and its pathogenesis and clinical significance are unknown (Fig. 1).

Alopecia has also been found consistently in all but one case (not described in the case reported by Truwit et al.). In GLHS, alopecia is focal, bilateral, congenital, and predominantly located in the parieto-occipital region [4, 11, 14, 18, 19]. However, alopecia can be markedly asymmetric [15] or, as in one case, even unilateral [4]. Less frequent localizations are the temporal (as in most cases of this series), frontoparietal, frontotemporoparietal, or temporo-parietal regions. One patient in this report had bitemporal alopecia with additional small areas of alopecia anteriorly and on the region of the vertex (Fig. 2). Similar additional alopecia areas have not been previously reported. In some cases, alopecia may be easily concealed by the surrounding scalp hair and must be carefully looked for.

All the other clinical and neurological signs and findings do not occur consistently in published GLHS cases, as well as in the cases reported here.

Trigeminal anesthesia most often affects the ophthalmic branch, causing abnormal sensation of the forehead and cornea, and may result in frontal scars and corneal opacities. Trigeminal anesthesia was absent in four of 21 cases [2, 6, 15, 17]. In the present series, all patients had normal forehead sensation and corneal reflexes.

Ataxia (truncal and/or limb) and muscular hypotonia are the most common neurological manifestations of rhombencephalosynapsis and GLHS [14, 22]. These symptoms can

vary considerably in severity but are mostly mild, and only a few patients are partly restricted in daily life activities. So far, ataxia was present in 17 reported cases, muscular hypotonia in ten. However, only one patient in this report presented with mild truncal and limb ataxia, while muscular hypotonia was detectable in four of six cases. Therefore, both ataxia and muscular hypotonia are frequent, but inconsistent, findings in GLHS.

Head nodding stereotypies consist of side-to-side “no” movements, up-and-down “yes” movements, or shoulder-to-shoulder resembling an infinite sign [1, 7]. The resulting disruption may severely interfere with social skills, particularly in children with normal cognitive functions. Head nodding has been reported in six patients with GLHS [3, 15, 20, 25] and was present in four of six children in this report. It is probably underrecognized. Head nodding has also been reported in nonsyndromic rhombencephalosynapsis [14] and other cerebellar abnormalities such as unilateral cerebellar hypoplasia [8, 16].

Cognitive impairment to a varying degree has been found in most (13 of 21) previously reported patients.

Table 2 Clinical and neuroimaging findings in Gómez–López–Hernández syndrome

Consistent	Not consistent
Rhombencephalosynapsis	Trigeminal anesthesia
Alopecia	Ataxia (truncal and/or limb)
	Cognitive impairment
	Brachy-turriccephaly
	Midface hypoplasia
	Hypertelorism
	Low-set, posteriorly rotated ears
	Strabismus

However, four patients [11, 15, 17, 23] as well as three of this report showed normal cognitive functions. Long-term cognitive outcome is also variable in nonsyndromic rhombencephalosynapsis, but cognitive functions are usually impaired [14]. Nevertheless, both nonsyndromic rhombencephalosynapsis and GLHS are compatible with a favorable cognitive outcome in some cases.

Craniofacial phenotype in GLHS typically includes midface hypoplasia, turri- and/or brachycephaly, low-set and posteriorly rotated ears, hypertelorism, and strabismus. These dysmorphic signs are present in most, but not all, cases (as in patient 6 of this report).

Most reported patients with GLHS are not associated with other diseases. In our previous series, one patient suffered from neurogenic bladder dysfunction and another from esophageal atresia [15]. In this series, one patient had cryptorchidism and another agenesis of the right kidney. Renal agenesis has been also reported by Pasquier et al. in one fetal case of rhombencephalosynapsis [13].

In conclusion, only RS and alopecia are consistently present in all GLHS cases and are crucial for the diagnosis (Table 2). Both the term *cerebellotrigeminal* dermal dysplasia and the admission of incomplete forms without rhombencephalosynapsis or alopecia (as proposed by Fernandez-Jaen et al. [4]) are potentially misleading. Rhombencephalosynapsis can be diagnosed by fetal MRI [12, 20]. However, GLHS can only be diagnosed after birth, as alopecia is only detectable postnatally. In all patients with rhombencephalosynapsis, alopecia must be painstakingly sought (can easily be hidden), and rhombencephalosynapsis must be sought if congenital alopecia is present. Otherwise, the diagnosis of GLHS can easily be missed.

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Conflict of interest None of the authors have any conflict of interest.

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